Recludix Pharma

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Oral selective STAT3 inhibitors demonstrate differentiated efficacy and safety potential in preclinical models of Th17 mediated skin inflammation

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Disclosures

Employees and/or shareholders of Recludix Pharma

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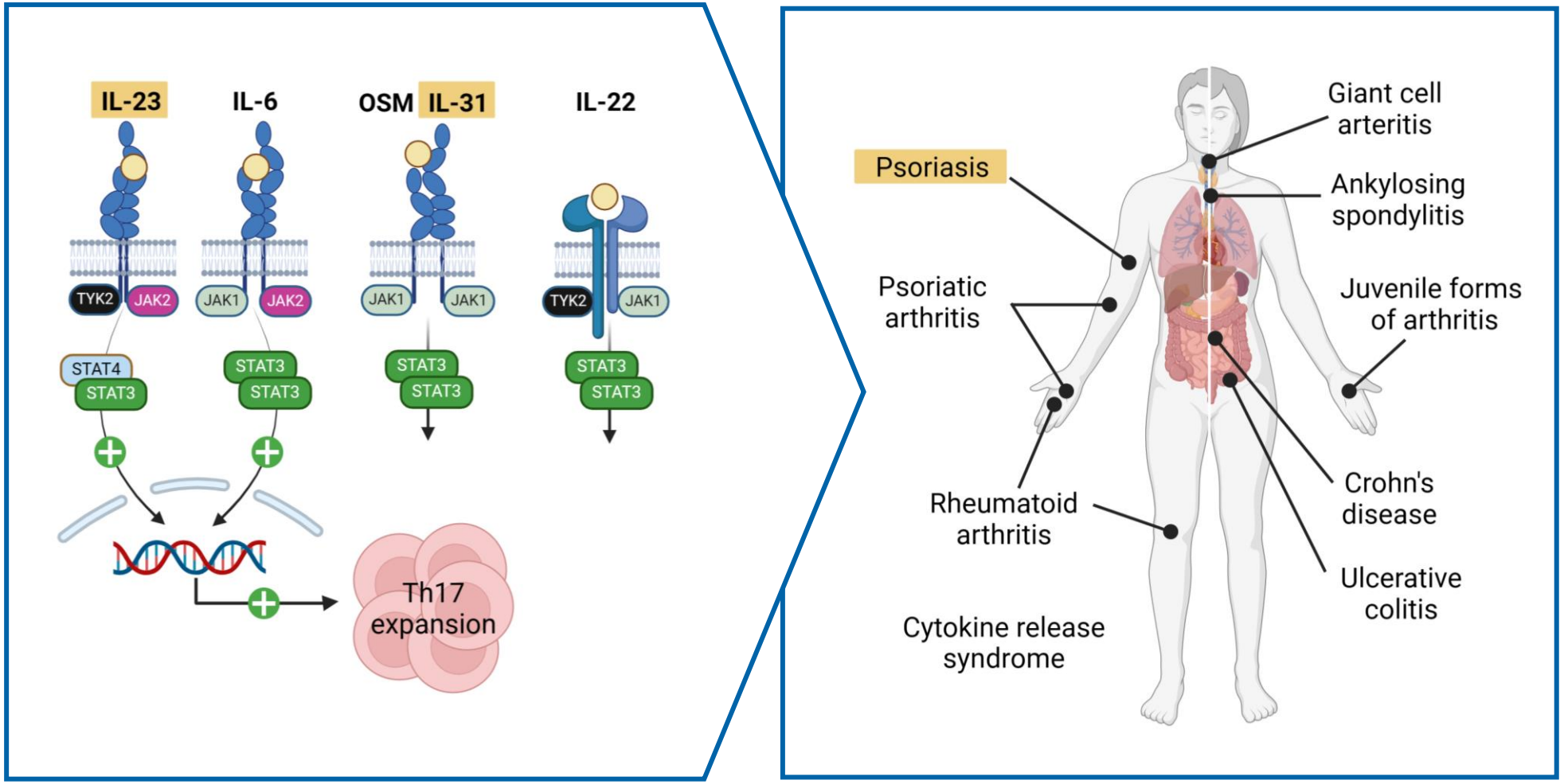
No Disclosures

Dr. Seong Kim

STAT3 Inhibition Has Potential Clinical Applications Across Multiple Inflammatory and Autoimmune Diseases



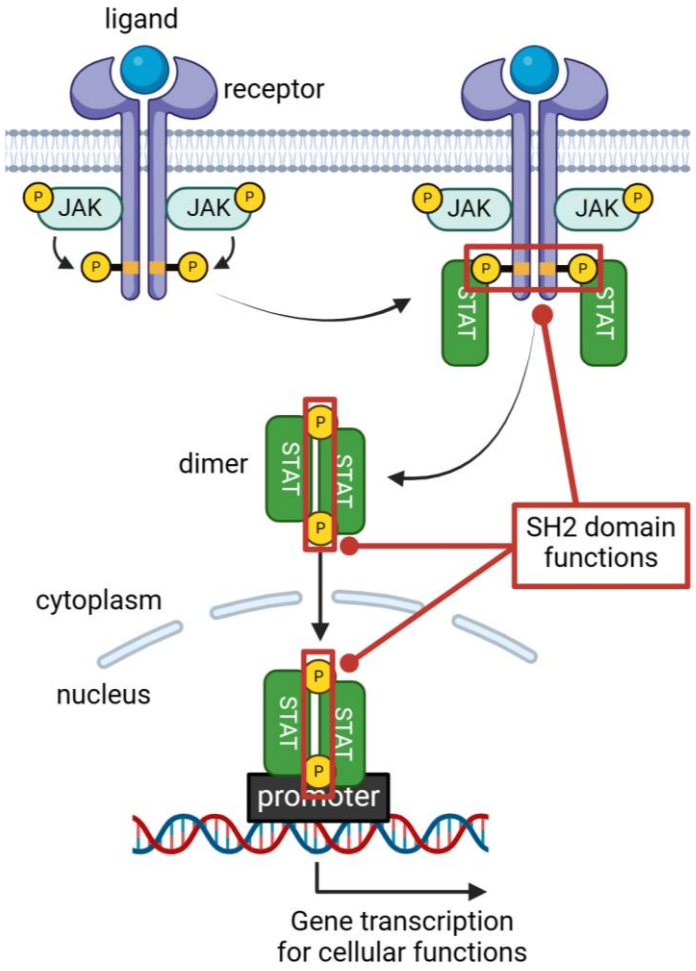
Small molecule STAT3 inhibitors may provide an oral alternative to clinically validated biologics

SH2 Domains Have Previously Been Deemed “Undruggable”

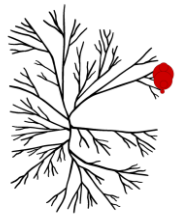
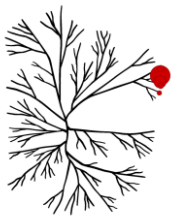
Src Homology 2 (SH2) domains are highly conserved protein domains that have long been recognized as attractive drug targets

- Small protein modules made up of ~100 amino acids
- 120 human SH2 domains
- The SH2 domain of STAT proteins is required for;
  - Binding to cytokine receptors via the SH2 domain and phospho-tyrosine motifs on the receptor
  - Dimerization of STAT proteins occurs by reciprocal interactions with each monomer's SH2 domain; STAT DNA binding and transcriptional activity requires dimerization

Recludix has created a platform of integrated technologies enabling SH2 domain inhibitor discovery



Recludix Has Discovered Highly Potent, Selective, Orally Available STAT3 Inhibitors

	REX-5376	REX-7117
Biochemical Potency (SH2scan K_D)	0.15 nM	0.15 nM
Cellular Potency (pSTAT3 IC_{50} in human PBMCs, 20hrs)	0.7 nM	1.1 nM
Cellular Selectivity (PBMCs)	~1-2X vs. STAT1 >150X vs. STAT2/4 >1,000X vs. STAT5/6	~20X vs. STAT1 >20-30X vs. STAT2 >1,000X vs. STAT4/5/6
SH2 Family Selectivity		

STAT3 potency and selectivity maintained across biochemical and cellular assays

STAT3 Inhibitors Impair Th17 Cell Function with Differentiated Selectivity From JAK/TYK2 Inhibitors

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Primary human T cells cultured under Thelper (Th) skewing conditions in the presence of compounds

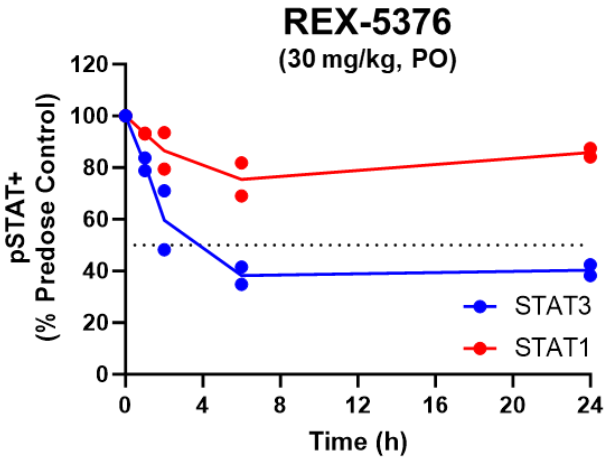
		T cell function			
		General Adaptive Immune response	Defense against viruses and bacteria	Defense against extracellular pathogens	Defense against parasites and mediation of antibody responses
		T Cell Activation (CD25 IC_{50})	Th1 Cell Function (IFNγ IC_{50})	Th17 Cell Function (IL-17A IC_{50})	Th2 Cell Function (IL-5 IC_{50})
	REX-7117	**>10,000 nM**	**>3,000 nM**	**14 nM**	**>3,000 nM**
	REX-5376	**>10,000 nM**	**>2,000 nM**	**11 nM**	**>3,000 nM**
TYK2 Inhibitors	Deucravacitinib	>3,000 nM	260 nM	**34 nM**	~3,300 nM
	TAK-279	>10,000 nM	69 nM	**47 nM**	>3,000 nM
JAK Inhibitors	Tofacitinib	340 nM	74 nM	**20 nM**	20 nM
	Upadacitinib	39 nM	36 nM	**8 nM**	4 nM
	Baricitinib	110 nM	210 nM	**15 nM**	15 nM

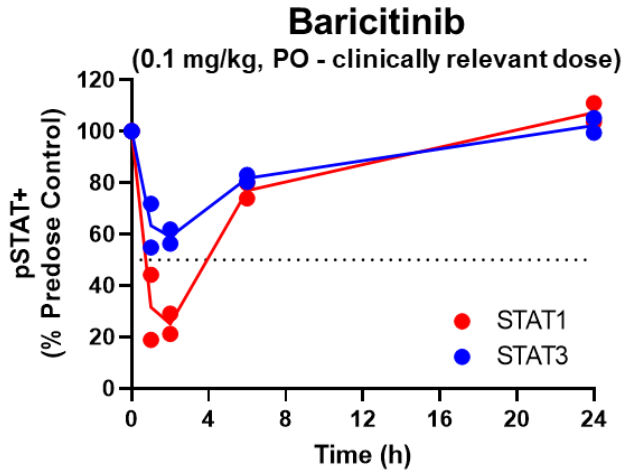
Selectivity relative to Th17 inhibition: >30X 10-30X <10X

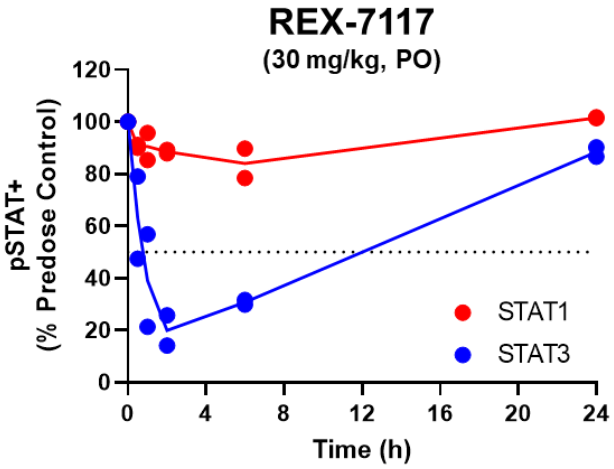
Targeting STAT3 uniquely spares the broader T cell compartment

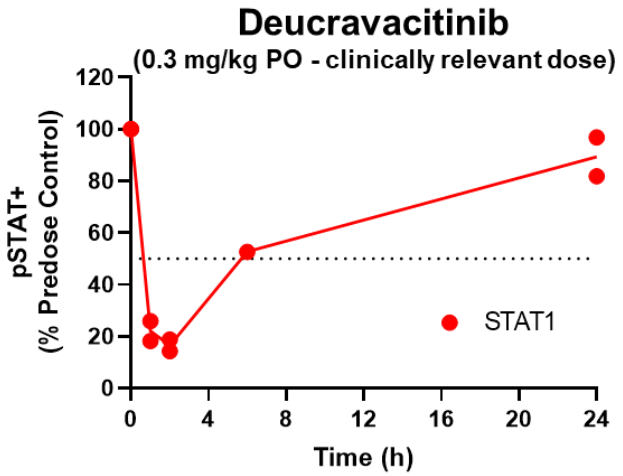
Oral STAT3 Compounds in Dogs Achieve *In Vivo* Selective and Sustained Target Inhibition

Dog PBMCs evaluated for STAT inhibition following single day oral dosing







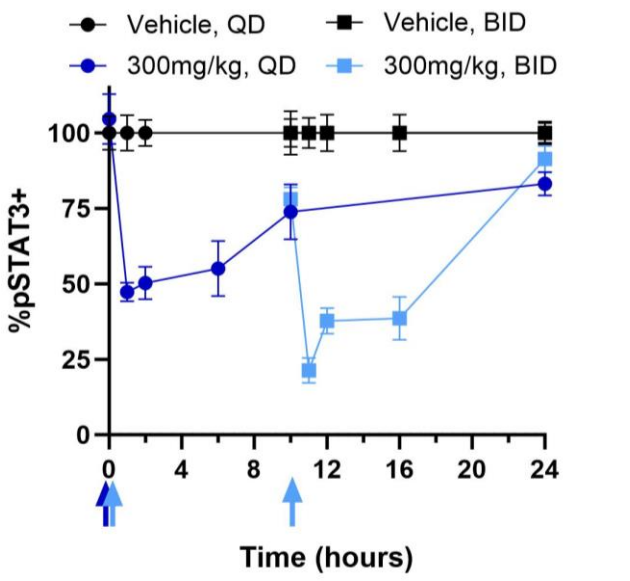


REX-7117 Inhibits on-target STAT3 activation but spares STAT1 mediated signaling

REX-7117 Demonstrates Efficacy After Oral Dosing in a Murine IL-23-Induced Th17 Model of Psoriasis

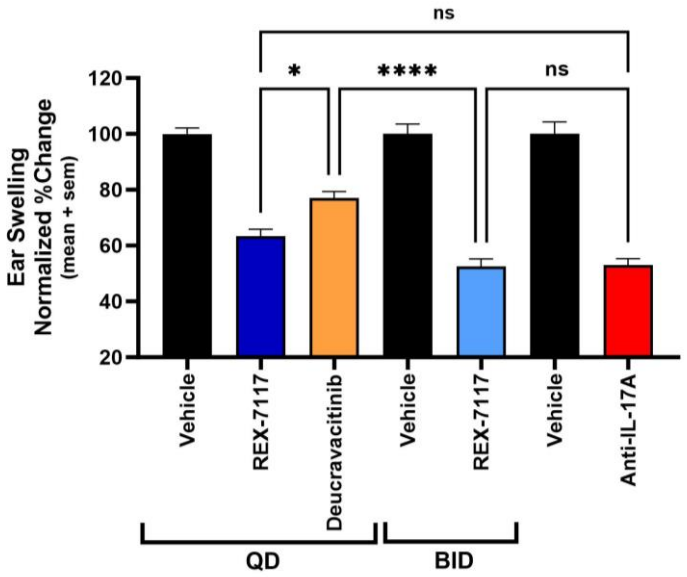
- Preclinical model used in the development of anti-IL-17 and anti-IL-23 biologics therapies
- REX-7117 dose was selected to match PD profile to that observed in dog at 15 mg/kg QD
- Deucravacitinib clinically relevant dose determined from regulatory filings and publications

Mouse pSTAT3 Inhibiton



n = 8-13 per timepoint

IL-23 Induced Psoriasis Model

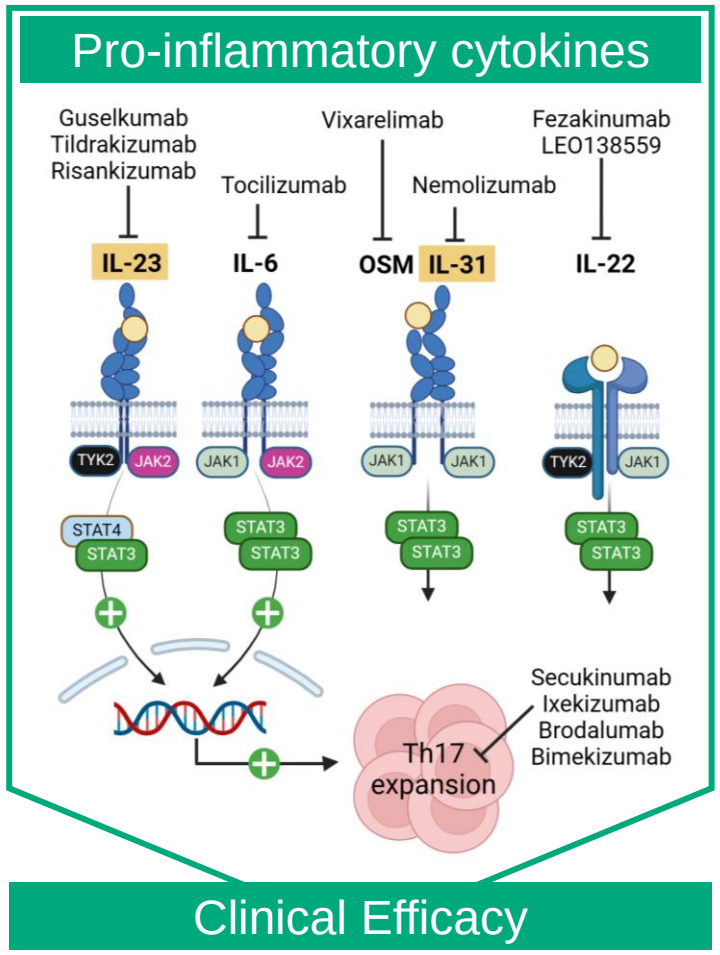


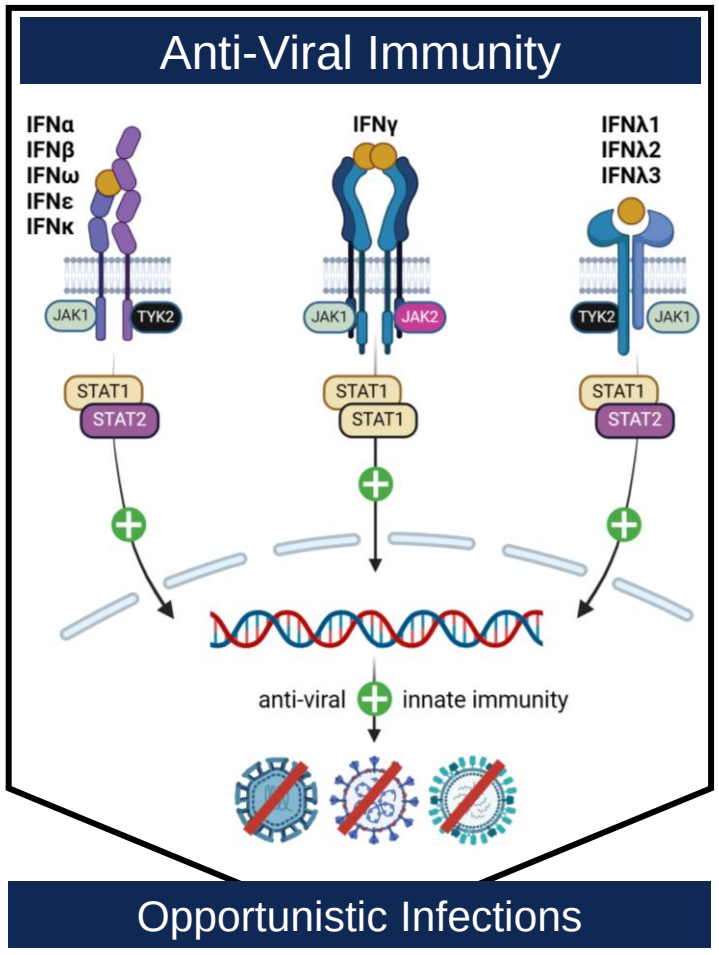
Deucravacitinib 1mg/kg is the estimated clinically relevant dose
Anti-IL-17A = Mouse surrogates of Cosentyx®

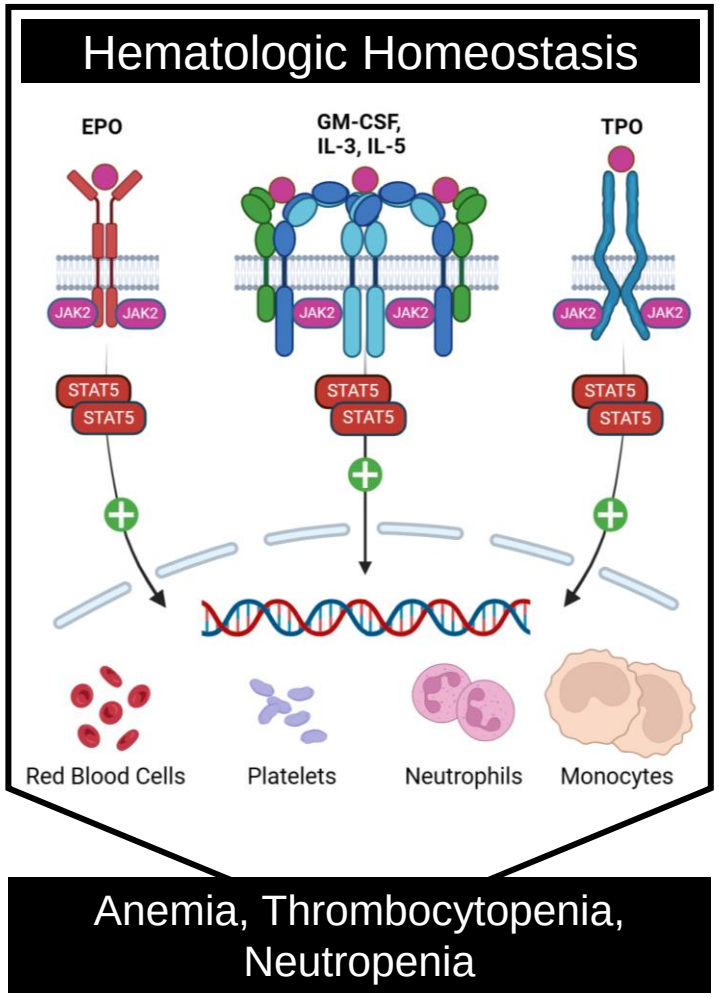
*P < 0.05
****P < 0.0001
ns – not significant

REX-7117 efficacy comparable to anti-IL-17A biologic and improved relative to deucravacitinib

STAT3 Inhibition Selectively Targets Key Inflammatory Cytokines and Downstream Th17 Cell Pathogenesis







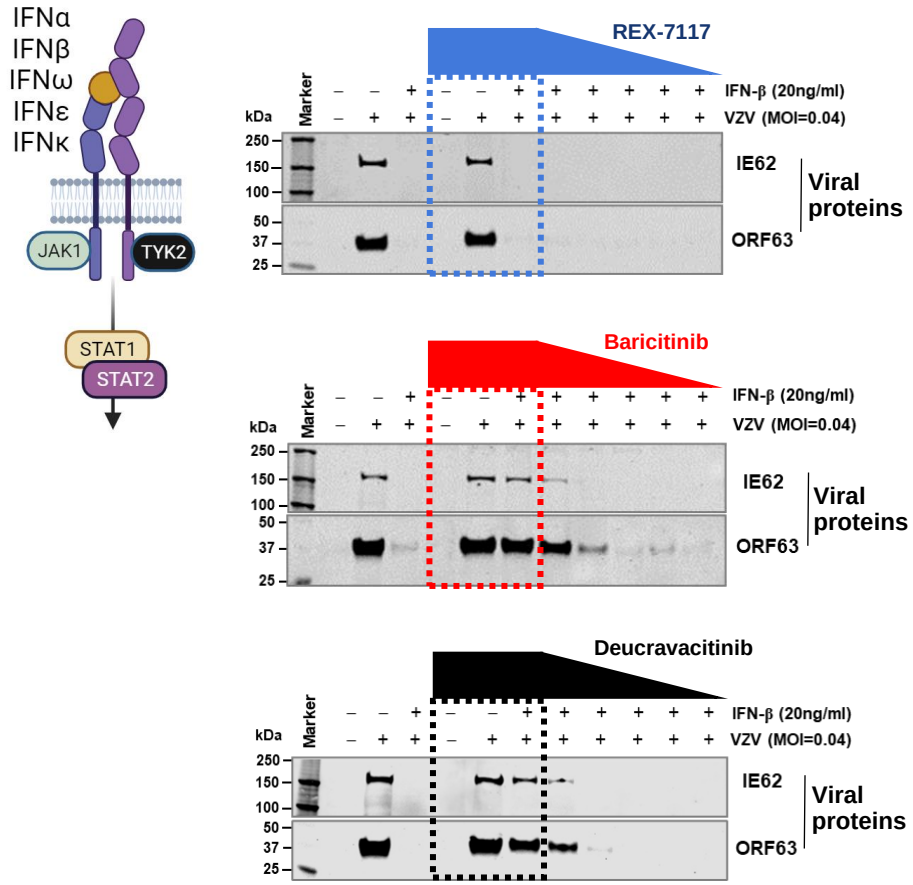
Selective STAT3 inhibitors have potential JAK/TYK2 safety differentiation advantages

Selectively Targeting STAT3 Does Not Impair Interferon-Mediated Inhibition of VZV Viral Replication

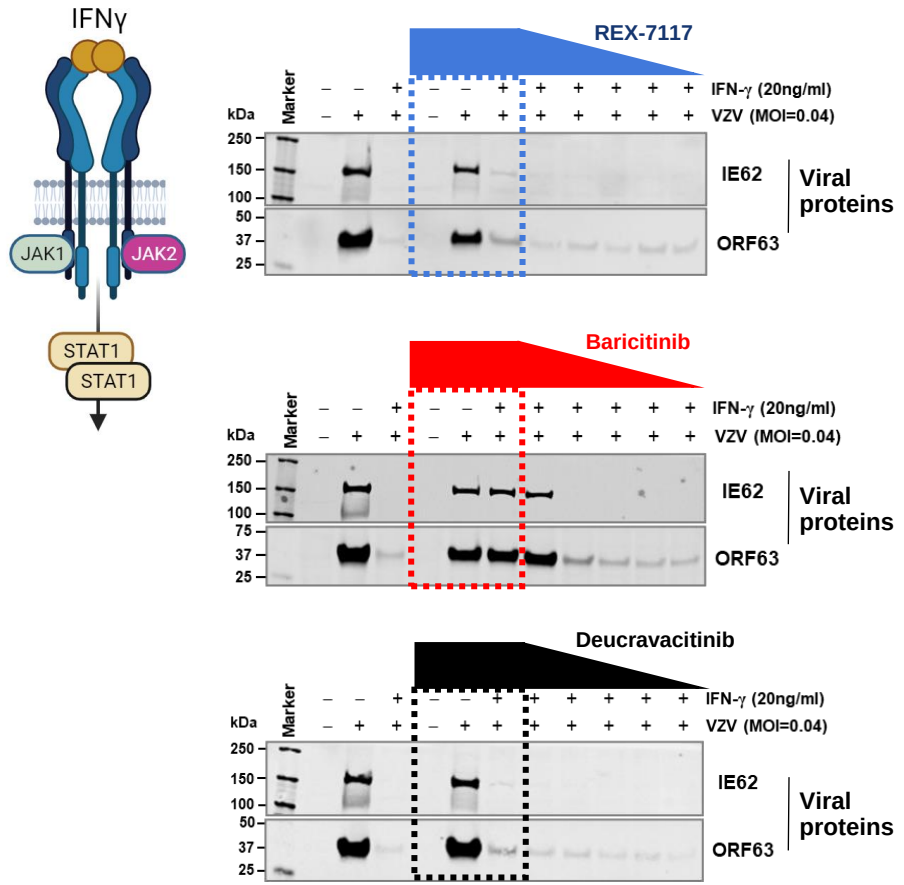
Human retinal epithelial cells preincubated with STAT3 or JAK/TYK2 inhibitors then either IFNβ or IFNγ cytokines, followed by VZV infection.

Measurement of viral IE62 and ORF63 protein expression 48hrs post-infection

Type I IFN: Herpes Zoster



Type II IFN: Herpes Zoster



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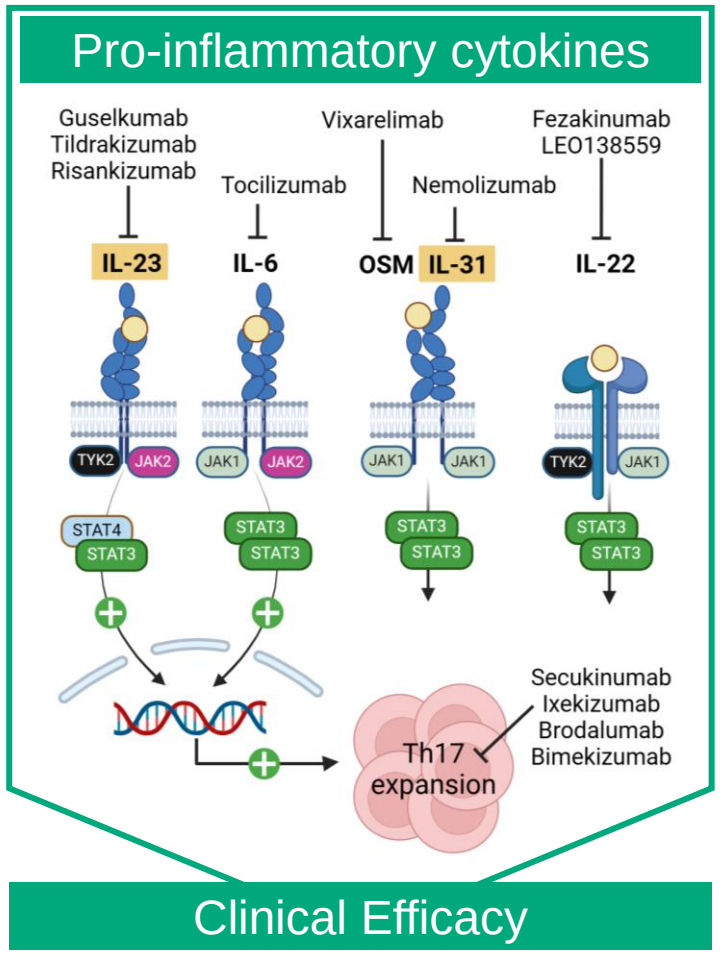
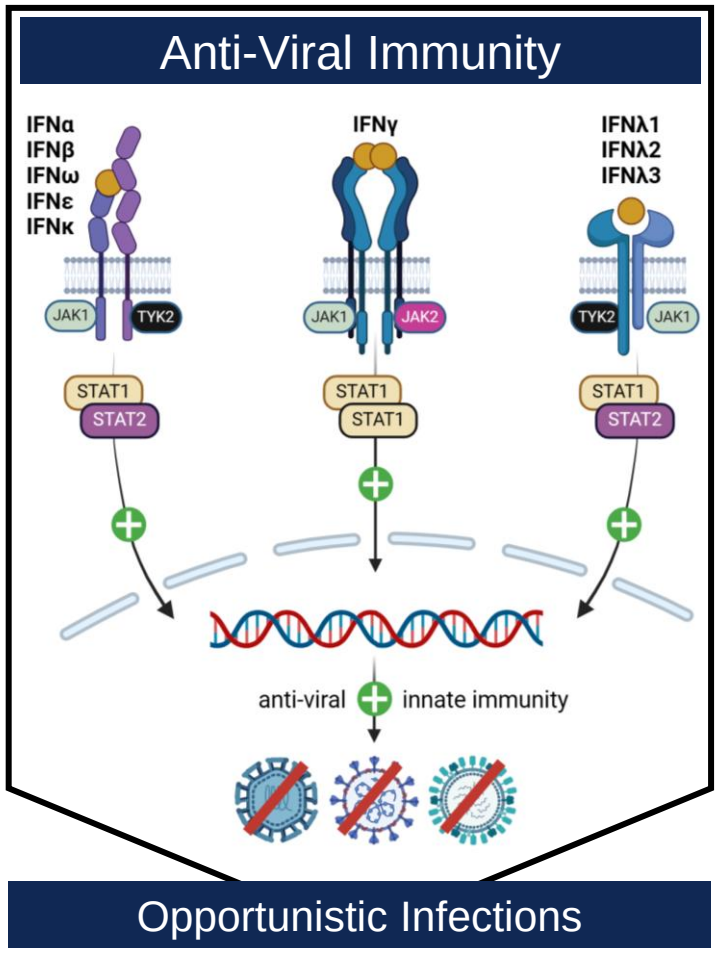
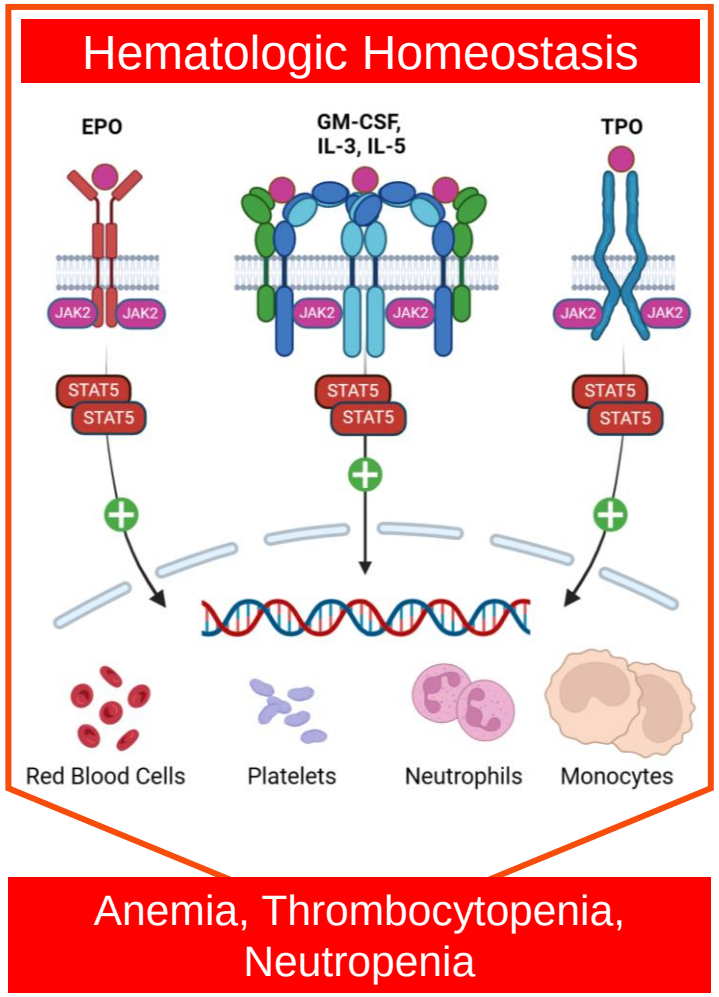
STAT3 inhibition spares IFN dependent anti-viral immunity and differentiates from JAK/TYK2 therapies

STAT3 Inhibition Selectively Targets Key Inflammatory Cytokines and Downstream Th17 Cell Pathogenesis



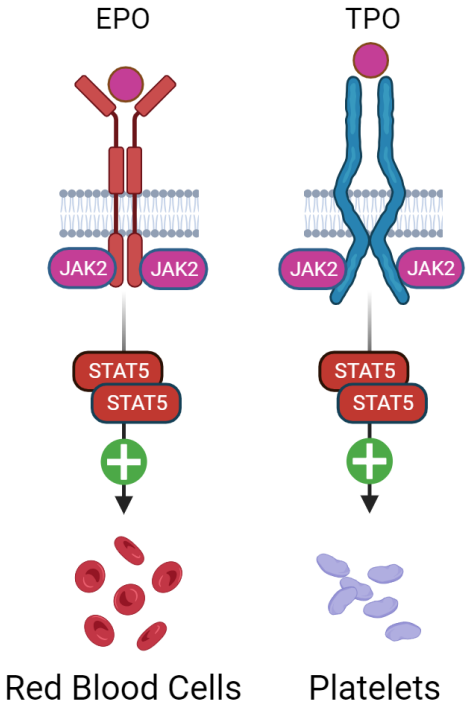




Selective STAT3 inhibitors have potential JAK/TYK2 safety differentiation advantages

Targeting STAT3 Spares STAT5 Mediated Hematopoietic Signaling

Hematology Homeostasis



Erythropoietin (EPO) or Thrombopoietin (TPO) mediated pSTAT5 signaling in reporter cell lines		STAT3-driven Inflammation	Hematopoiesis	
			Erythropoiesis	Thrombopoiesis
		IL-6-Driven pSTAT3 Activation in PBMCs (IC_{50})	EPO-Induced STAT5-Driven Transcription (IC_{50})	TPO-Induced STAT5-Driven Transcription (IC_{50})
STAT3 Inhibitors	**REX-5376**	**6 nM**	**>10,000 nM**	**>10,000 nM**
	REX-7117	**1 nM**	**>10,000 nM**	**>10,000 nM**
TYK2 Inhibitors	Deucravacitinib	**140 nM**	3,200 nM	250 nM
	TAK-279	**>10,000 nM**	>10,000 nM	>10,000 nM
JAK Inhibitors	Tofacitinib	**110 nM**	340 nM	200 nM
	Upadacitinib	**48 nM**	69 nM	20 nM
	Baricitinib	**28 nM**	55 nM	46 nM

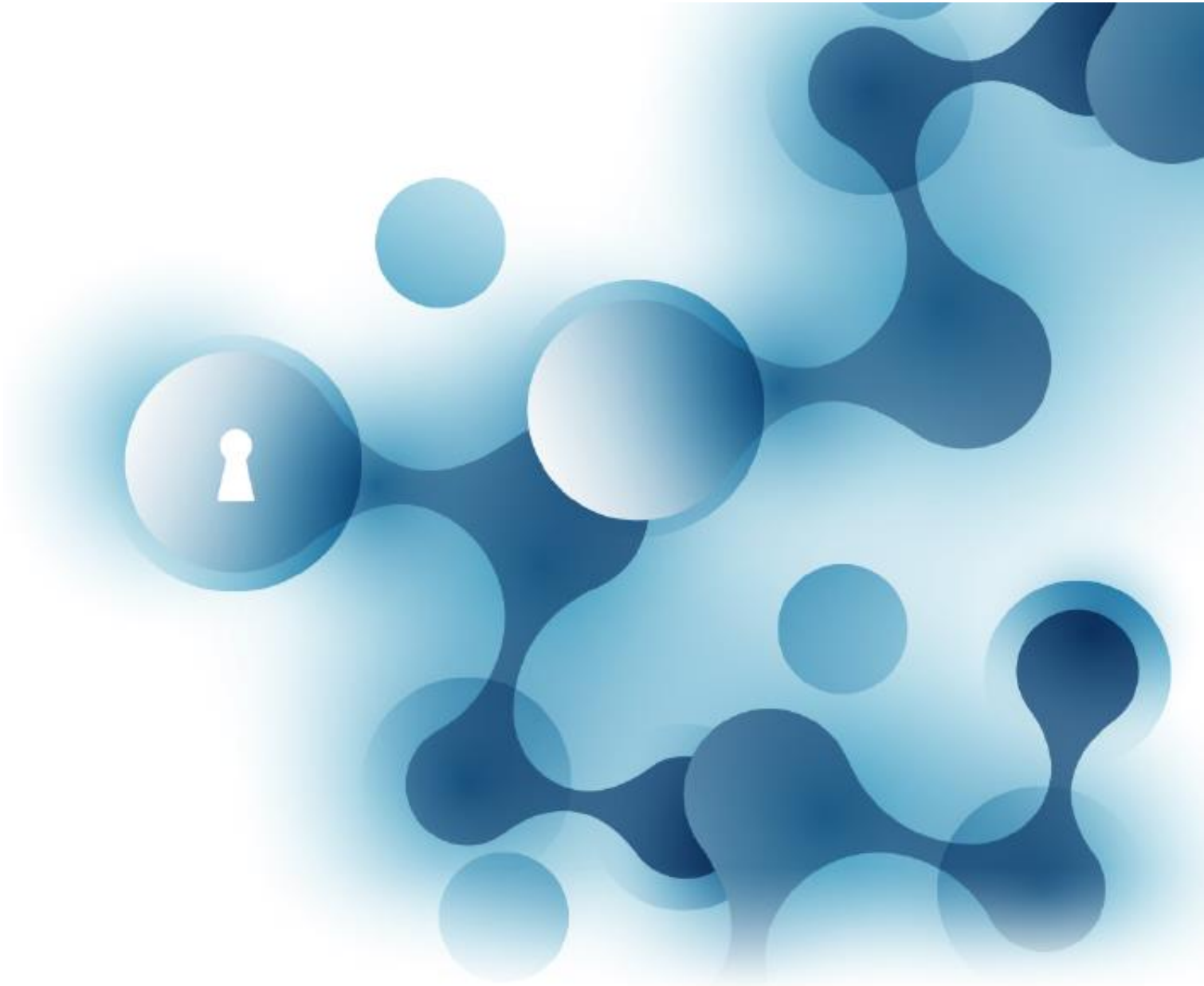
Selectivity relative to PBMC pSTAT3 inhibition: >30X 10-30X <10X

JAK inhibitors impair hematopoietic signaling at equivalent concentrations to their anti-inflammatory mechanism of action

Oral Selective STAT Inhibitors Offer The Potential For Biologics-Like Safety & Efficacy

- Recludix has generated orally available, potent and selective small molecule STAT3 inhibitors active against Th17 driven inflammation
- Selective STAT3 targeting has the potential for both enhanced efficacy and safety relative to JAK/TYK2 family inhibitors
- STAT3 inhibition has potential clinical applications across Th17 driven diseases, including Psoriasis, Psoriatic Arthritis, Rheumatoid Arthritis, and Inflammatory Bowel Disease
- Recludix has created a discovery platform integrating multiple technologies facilitates drugging of previously ‘undruggable’ targets, including other STAT family members

Please visit poster #738 in Poster Session 2



Thank you

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